REMARKS

I. Status of the Claims

Claims 1-33 are pending in this application. Claims 1-26 have been canceled. Claims 27-33 have been amended.

Although the Examiner notes that he has conducted a search only for claims 1, 11, 19, and 20-21 (*Office Action* at p. 3, 3rd ¶), Applicants note that none of the claims have been withdrawn from consideration nor have any of the claims been subjected to a restriction requirement according to the Office Action Summary. Moreover, Applicants note that the Examiner had rejected claims 1, 12, 19, 20-23, 24, 25, "and claims dependent on these claims" under 35 U.S.C. § 102(b). (*Office Action* at p. 4, §§ 8-9.) Accordingly, it appears that the Examiner has considered all of the originally filed claims. Applicants respectfully request consideration of claims 27-33, which depended from claims 1 and/or 12 and remain pending in the application after cancellation of claims 1-26.

Claim 27 has been rewritten in independent form to incorporate the limitations of cancelled claim 1, from which it previously depended. Claim 27, as amended, is directed to a compound of formula I wherein R^1 is haloalkyl; R^2 is haloalkyl; R^3 is trans-cinnamide wherein R^8 and R^9 are hydrogen and R^{10} and R^{11} together are heterocyclyl; R^4 is hydrogen; R^5 is hydrogen; and **Ar** is aryl, wherein the aryl is substituted with substituted heterocyclyl. Claim 28, which previously depended from claim 1, has been amended to depend from claim 27. Claims 29-31, which previously depended from claim 12, has been amended to depend from claim 28.

Claim 32 has been amended to incorporate the limitations of cancelled claim 1, from which it previously depended. Claim 33 has been amended to depend from claim 32.

II. Objections

The Examiner suggests language for claiming the benefit of priority to previous applications. (*Id.* at p. 2.) Applicants respectfully submit that the benefit of priority has been amended at section 9 of the transmittal letter accompanying the filing of the application. The amended language is similar to that suggested by the Examiner. Accordingly, Applicants respectfully submit that the benefit of priority claim is proper.

The Examiner suggests that Applicants should also claim of priority from U.S. Application No. 09/222,491, filed December 29, 1998. Applicants note that the '491 application is not a related application. The '491 application was filed as a separate application on the same day as provisional U.S. Application No. 60/114,097, from which the present application claims the benefit of priority.

The Examiner requests the nature of the relationship of PCT Application Nos. PCT/US99/31162 and PCT/US00/08895. The PCT '162 application published as WO 00/29081 and claims priority to the '491 application. As explained above, the '491 application is not a related application. The PCT '895 application published as WO 00/59880 and claims priority to U.S. Application Nos. 09/286,645 and 09/494,517. The present application claims the benefit of priority from the '517 application.

Accordingly, Applicants respectfully request withdrawal of this objection.

III. Examiner's Observations

The Examiner asserts that claims 24 and 25 are new and should be granted the priority date of the instant application. (*Office Action* at p. 2.) Applicants respectfully disagree and note that claims 24 and 25 are identical to claims 24 and 25 of grandparent Application No. 09/541,795, which was filed March 31, 2000, and claims 24 and 25 of parent Application No. 09/695,040, which was filed October 24, 2000. Thus, the subject matter of present claims 24 and 25 should be granted a priority date of March 31, 2000.

The Examiner also asserts that claims 32 and 33 should be granted the priority date of the instant application. (*Id.*) Applicants respectfully disagree and note that claims 32 and 33 are identical to claims 32 and 33 of parent Application No. 09/695,040, which was filed October 24, 2000. Thus, the subject matter of present claims 32 and 33 should be granted a priority date of October 24, 2000.

IV. Double Patenting Rejections

Claims 1, 19, 20-23 "and claims dependent on these claims" are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 15, 16-19 of U.S. Patent No. 6,110,922. (*Id.* at p. 3.)

Claims 1, 19, 20-23 "and claims dependent on these claims" are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-15, 16-19, 29, 30, 32, 35, and 37 "and claims dependent on these claims" of copending Application No. 10/356,794. (*Id.* at pp. 3-4.)

Claims 1, 19, 20-23, 24, and 25 "and claims dependent on these claims" are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 19, 20-25, and 45-51 "and claims dependent on these claims" of copending Application No. 09/541,795. (*Id.* at p. 4.)

Claims 1, 19, 20-23, 24, and 25 "and claims dependent on these claims" are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 19, 20-25, 32, 33 "and claims dependent on these claims" of copending Application No. 09/695,040. (*Id.*)

Applicants respectfully request that these rejections be held in abeyance until allowable subject matter has been indicated.

V. Rejections Under 35 U.S.C. § 102(b)

Claims 1, 12, 19, 20-23, 24, 25, "and claims dependent on these claims" are rejected under 35 U.S.C. § 102(b) as being anticipated by:

1. "Franke," *Helvetica Chimica Acta*, Vol. 58, pp. 268-78 (1975)
2. "Ohno," GB 2117760;
3. "Bernardon 423," WO 98/22423;
4. "Greenspan," WO 98/13347;
5. "Bernardon 928," EP 722928;
6. "Miyamoto," EP 081321;
7. "Andree," DE 4030041; and
8. "Drews," EP 459243.

(*Office Action* at pp. 5-6.) Applicants respectfully traverse this rejection.

As discussed above, claims 1-26 have been cancelled. Independent compound claim 27, as amended, is a compound of formula I wherein R^1 is haloalkyl; R^2 is haloalkyl; R^3 is trans-cinnamide wherein R^8 and R^9 are hydrogen and R^{10} and R^{11} together are heterocyclyl; R^4 is hydrogen; R^5 is hydrogen; and **Ar** is aryl, wherein the aryl is substituted with a substituted heterocyclyl.

Franke discloses a diaryl sulfide compound (compound 49) where the groups corresponding to R^1 and R^2 of the claimed compositions are both hydrogen. (*Franke* at p. 18.) Thus, Franke's compound does not anticipate claim 27, which requires R^1 and R^2 to be a haloalkyl.

Ohno describes pyridyl compounds, where the pyridyl is bonded to an X group, which in turn is bonded to a phenyl. (*Ohno* at abstract.) Even if X were selected to be a sulfide, Ohno's pyridyl does not fall within the definition of **Ar** as recited in claim 27, where Ar is defined as a mono- or bicyclic carbocyclic aromatic ring. A pyridyl is not a carbocyclic ring.

Bernardon '423 discloses compounds having a phenyl ring linked to an aryl ring (Ar) by X. (*Bernardon '423* at abstract.) X can be oxygen or sulfur, among numerous other groups. (*Id.* at p. 2, line 24 to p. 3, line 4.) Bernardon '423 also teaches that Ar is substituted with Y, which can be an alkenyl or alkynyl radical as represented by formulas (a) and (b). (*Id.* at p. 2, lines 1-5.) However, Bernardon '423 does not provide any guidance that would lead one of ordinary skill in the art to select the groups that would form a cinnamide at the corresponding R^3 position. Diaryl sulfide cinnamides are

not specifically disclosed. Moreover, even if X were chosen to be sulfur, the groups corresponding to R^1 and R^2 are not haloalkyls, as required by claim 27.

Greenspan discloses compounds of formula (I) having a six-membered C_5W ring, where W can be CH or N and the ring is substituted with a cinnamide. (*Greenspan* at abstract.) The C_5W ring can also be substituted with X-Y-X and X^1-R, where X and X^1 can be O, S, SO, SO_2, or a direct bond. (*Id.*) Again, even if X were chosen to be sulfur, the groups corresponding to R^1 and R^2 are not haloalkyls, as required by claim 27.

Bernardon '928 discloses compounds having two substituted phenyl rings linked by X, where X can be -O-, $-S(O)_t-$, or $-NR_{12}-$. (*Bernardon '928* at abstract and p. 3, lines 20-21.) Bernardon '928 further teaches that one phenyl ring contains an optionally substituted alkene group *para* to X. (*Id.* at abstract.) However, Bernardon '928 does not provide any guidance that would lead one of ordinary skill in the art to select the groups that would form a cinnamide at the corresponding R^3 position. Diaryl sulfide cinnamides are not specifically disclosed. Moreover, even if X were chosen to be sulfur, the groups corresponding to R^1 and R^2 are not haloalkyls, as required by claim 27.

Andree discloses compounds having a phenyl ring substituted with Q^1 and Q^2 groups positioned meta to each other. (*Andree* at abstract.) Q^1 and Q^2 can be O, S, NH, or N-alkyl bonded to a 1,3,5-triazine, wherein the 1,3,5-triazine is optionally substituted. (*Id.*) Assuming for the sake of argument that Q^1 or Q^2 is chosen to be sulfur, Andree fails to teach a cinnamide at the corresponding R^3 position.

Miyamoto discloses 2-aminophenol compounds substituted with R_1 and -Z-CO_2-R_2. (*Miyamoto* at p. 9.) One of many substituent choices for R_1 is -S-phenyl, in which the phenyl is *para*-substituted with R_4. (*Id.*) However, no combination of Z and R_2 substituents will result in a cinnamide group.

Drews teaches heterocyclyl azine groups linked to a phenyl through Q, which may be O or S. (*Drews* at p. 3.) The heterocyclylic azine, however, would not fall within the definition of **Ar** as recited in claim 27, where Ar is defined as a mono- or bicyclic carbocyclic aromatic ring. A heterocyclylic azine is not a carbocyclic ring.

Thus, Applicants respectfully submit that none of the cited references disclose a compound of formula I having the specific R^1-R^5 and R^8-R^{11} groups recited in claim 27, or in dependent claims 28-31.

Claims 32 and 33 are directed to a method of treating cerebral vasospasm with a compound of formula I or a composition comprising the compound of formula I. None of the cited references disclose a method of treating cerebral vasospasm.

Accordingly, the cited references do not anticipate claims 27-33. Applicants respectfully request withdrawal of this rejection.

VI. Rejections Under 35 U.S.C. § 112, second paragraph

Claims 1, 12, 13, 19, and 20-23 are rejected under 35 U.S.C. § 112, second paragraph as being indefinite. (*Office Action* at pp. 6-7.) Applicants respectfully traverse this rejection as follows.

Because claims 1-26 have been cancelled, any rejections pertaining to these claims are moot and thus, are not addressed here.

The Examiner alleges that the terms "aryl" and "heterocyclyl" are indefinite as not being specified to number, size, heteroatom content and other parameters. (*Id.* at p. 6.) Applicants respectfully submit that "aryl" and "heterocyclyl" have well known meanings in the art. Nonetheless, to expedite prosecution, Applicants have added definitions of "aryl" and "heterocyclyl" in independent claims 27 and 31. Support for the definition of "aryl" can be found in the specification at p. 9, lines 26-30, and that of "heterocyclyl" at p. 10, line 24, to p. 11, line 17.

Regarding claims 32 and 33, the Examiner alleges that "administration of a compound or composition" is indefinite and suggests use of the language "administration of a therapeutically effective amount of a compound" or composition. (*Id.*) While Applicants respectfully disagree that "administration of a compound" is indefinite, independent claim 32 has been amended to incorporate the Examiner's suggested language.

The Examiner also alleges that claims 32 and 33 are indefinite because they "do not exactly and definitively recite the mode of administration." (*Id.*) While Applicants respectfully disagree, independent claim 32 has been amended to recite "wherein the compound is administered orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically, bucally, or as an oral or nasal spray." Support for this amendment can be found in the specification at p. 39, lines 4-7.

The Examiner also alleges that "cerebral vasospasm" renders claims 32 and 33 indefinite because the claims are silent "on what is exactly and definitely included or excluded from the stated disease or response." (*Id.*) Applicants respectfully disagree. The standard of definiteness under 35 U.S.C. § 112, second paragraph, is a reasonable

degree of clarity and precision. (M.P.E.P. § 2173.02.) "Definiteness of claim language must be analyzed, not in a vacuum, but in light of:

(A) The content of the particular application disclosure;

(B) The teachings of the prior art; and

(C) The claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made."

(*Id.*)

Applicants respectfully submit that "cerebral vasospasm" would be understood by one of ordinary skill in the art because each word, *i.e.*, "cerebral" and "vasospasm" has a well-known meaning in the art. It is well-settled law that a common meaning of a phrase can be derived by determining the "established meanings of the individual words." *Altiris, Inc. v. Symantec Corp.*, 318 F.3d 1363, 1372, 65 U.S.P.Q.2d 1865, 1871 (Fed. Cir. 2003). "Cerebral" is defined as "relating to the cerebrum," which in itself has a well-known meaning. (Stedman's Medical Dictionary, 27th edition, Lippinscott Williams & Willkis, 1999.) "Vasospasm" is defined as a contraction of the muscular coats of the blood vessels. (*Id.*) Thus, the meaning of "cerebral vasospasm" can be determined to be a contraction of the muscular coats of the blood vessels of the cerebrum.

Moreover, Applicants submit two papers as evidence that "cerebral vasospasm" is a commonly known term of art. (Clatterbuck et al., *J. Neurosurg.*, Vol. 97, pp. 676-82, 2002 ("Clatterbuck 2002"); Pradilla et al., *J. Neurosurg.*, Vol. 101, pp. 88-91, 2004 ("Pradilla").) Based on this evidence, Applicants respectfully submit that the meaning of

"cerebral vasospasm" is sufficiently definite to one of ordinary skill in the art to satisfy § 112, second paragraph.

The Examiner contends that the claims "remain silent about the biological/pharmacological activity with which the diseases or responses are associated." (*Id.*)

Applicants note that the Examiner has provided no rationale on why the failure to cite "biological/pharmacological activity" would render the claims indefinite. As stated above, claims 32 and 33 are claims directed to methods of treating cerebral vasospasm and recite various modes of administration. The meaning of each term is sufficiently clear to one of ordinary skill in the art.

Each of the terms recited in claims 32 and 33 has a well-known meaning in the art. The Examiner has not explained why failure to recite the biological/pharmacological activity renders claims 32 and 33 indefinite.

Accordingly, Applicants respectfully request withdrawal of this rejection.

VII. Rejections Under 35 U.S.C. § 112, first paragraph

Claims 20-23, 32, and 33 are rejected under 35 U.S.C. § 112, first paragraph as being nonenabling. (*Office Action* at pp. 7-11.) Applicants respectfully traverse this rejection as follows.

The specification describes assays that can be used to screen for agents having the ability to block the ICAM-1/LFA-1 interaction, such as an ICAM-1/LFA-1 biochemical interaction assay and an ICAM-1/JY-8 cell adhesion assay. (*Specification* at pp. 262-264.)

Applicants also submit the Clatterbuck 2002 and Pradilla papers to demonstrate the correlation between the activity of the claimed compounds towards I-CAM/LFA-1 inhibition and treatment of cerebral vasospasm. Clatterbuck 2003 is also submitted here. (Clatterbuck et al., *J. Neurosurg.*, Vol. 99, pp. 376-382, 2003). Pradilla states that "leukocyte-endothelial cell interactions, as mediated by CAMs, appear to play a major role in the development of posthemorrhagic cerebral vasospasm after aneurismal SAH" (subarachnoid hemorrhage). (*Pradilla* at p. 88.) Likewise, Clatterbuck 2002 states that inflammation "plays a crucial role in posthemorrhagic cerebral vasospasm." (*Clatterbuck* 2002 at p. 676.) Clatterbuck 2002 also discloses a model that could predict that blocking endothelial ICAM-1 interactions "would prevent vasospasm of cerebral vasculature." (*Id.* at p. 677.) Finally, Clatterbuck 2004 shows that the use of an antibody specific to inhibiting the ICAM-1/LFA-1 interaction "is effective in preventing cerebral vasospasm in nonhuman primates." (*Clatterbuck* 2004 at abstract.)

Based on the teachings of these three documents, Applicants respectfully submit that the treatment of cerebral vasospasm by the claimed compounds is sufficiently enabled. Accordingly, Applicants respectfully request withdrawal of this rejection.

VIII. Conclusion

In view of the foregoing amendments and remarks, Applicant respectfully requests reconsideration and reexamination of this application and the timely allowance of the pending claims. If the Examiner believes a telephone conference would be useful in resolving any outstanding issues, he is invited to call the undersigned at (617) 452-1621.

Application No.: 10/725,212
Attorney Docket No. 09095.0006-01

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

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Dated: September 7, 2004

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